

SUPPORTING INFORMATION

Why All The Fury Over Furin?

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Supplemental Table1. Proprotein convertase family members¹

PCSKs	Other names	Cleavage site specificity	Distribution in the organism	Subcellular compartments	Phenotypes of PC deficiency PC null mice	Human PC gene defects
PCSK1	PC1/3	K/RR↓	Pituitary	Secretory granules	Viable; pre- and postnatal lethality, dwarfism Hyper-proinsulinemia, chronic diarrhea	Obesity, impaired glucose homeostasis, impaired gastrointestinal function, hypogonatropic hypogonadism
PCSK2	PC2	K/RR↓	Pituitary	Secretory granules	Viable with retarded growth Hyperglycemia, endocrine peptides processing defects	
PCSK3	Furin PACE	RXXK/RR↓ RXXR↓ RXXRXXR/KR↓	Ubiquitous	TGN, endosome, cell surface, extracellular soluble furin	Lethal at day e10.5–11.5. multiple defects, i.e. failure of axial rotation, severe ventral closure defects	
PCSK4	PC4	KXXR↓ RXXK/RR↓	Testes, ovary, placenta	Plasma membrane	Viable Reduced fertility	
PCSK5	PC5/6A PC5/6B	RXXK/RR↓	PC5A: ubiquitous.	PC5A: Golgi, granules	PC5A: Postnatal death at days 4.5–7.5	PC5B: Embryo death at days e10.5–11.5
			PC5B: small intestine, kidney, liver, endocrine and non-endocrine cells	PC5B: TGN, endosomes, cell surface		

PCSK 6	PACE4	RXX/RR↓	Ubiquitous	TGN	75% mice are viable, 25% are lethal at days e13.5–15.5. Variable Phenotype, heart and situs defects, craniofacial malformations	
PCSK 7	PC7 PC8 LPC SPC7	RXX/RR↓	Ubiquitous	ER, TGN, cell surface	Viable; no phenotype change	
PCSK 8	SKI-1 S1P MBTPS 1	RX(V,L)(K,F,L) ↓	Ubiquitous	TGN, plasma membrane	Death in embryo state. Liver specific conditional SKI-1/S1P null mice are viable with reduced synthesis of cholesterol and fatty acids	
PCSK 9	NARC- 1	VFAQ↓SIP	Liver Drags LDLR to endosomes for degradation	TGN, cell surface	High LDLR and less insulin in pancreas than control mice.	hypoinsulinemic, hyperglycemic autosomal dominant hypercholesterolemia (ADH), a risk factor for coronary heart disease

Supplemental Table 2. Clinical trials related to furin

NCT	Phases	Enrollment	Start Date	Completion Date	Status	Study Results	Conditions	Interventions	Sponsor
NCT01061840	1	100	2009	2019	Completed	No	Ewing's Sarcoma Non-Small Cell Lung Cancer Liver Cancer	Vigil vaccine	Industry Gradalis, Inc.
NCT01453361	2	18	2011	2016	Terminated	Yes 2018	Advanced Melanoma	Vigil vaccine	Industry Gradalis, Inc.
NCT01551745	2	5	2012	2016	Completed	Yes 2018	Stage III and IV Ovarian Cancer	Vigil vaccine Bevacizumab	Industry Gradalis, Inc.
NCT01867086	2	1	2013	2016	Completed	Yes 2018	Stage III and IV Ovarian Cancer	Vigil vaccine Carboplatin Taxol	Industry Gradalis, Inc.
NCT03842865				Temporarily not available		No	Solid Tumor Ewing's Tumor Metastatic Ewing's Sarcoma Metastatic Advanced Gynecological Cancers: Ovarian Cervical Uterine Cancers	Vigil vaccine	Industry Gradalis, Inc.
NCT03073525	2	25	2017	2022	Active, not recruiting	No	Advanced Gynecological Cancers Ovarian Cancer Cervical Cancer Uterine Cancer	Vigil vaccine Atezolizumab	Industry Gradalis, Inc.
NCT03495921	3	114	2018	2023	Active, not recruiting	No	Ewing Sarcoma Metastatic Ewing's Sarcoma Connective and Soft Tissue Neoplasms	Vigil vaccine Irinotecan Temozolomide	Industry Gradalis, Inc.
NCT04687111	2	250	2015	2021	Active, not recruiting	No	Atrial Dilatation and Remodeling Left Ventricular Remodeling and Diastolic Dysfunction	Sacubitril Valsartan	Mark Ledwidge The Heartbeat Trust St Vincent's University Hospital

							Hypertension Diabetes Fibrosis Myocardial Inflammatory Myopathy Atrial Arrhythmia		
NCT02687191	1	21	2016	2018	Terminated	Yes 2019	Intracerebral Hemorrhage	PF-05230907	Industry Pfizer
NCT01174446	3	86	2010	2012	Completed	Yes 2013	Hemophilia B	BAX 326 (rFIX)	Industry Baxalta part of Shire
NCT01488994	2 and 3	23	2011	2013	Completed	Yes 2016	Hemophilia B	BAX 326	Industry Baxalta part of Shire
NCT03565237	4	25	2018	2021	Recruiting	No	Hemophilia B	RIXUBIS	Industry Baxalta part of Shire
NCT03879135	3	64	2019	2023	Recruiting	No	Von Willebrand Disease	Recombinant von Willebrand Factor (rVWF), rFVII	Industry Baxalta part of Shire
NCT02283268	3	24	2015	2016	Completed	Yes 2017	Von Willebrand Disease	rVWF	Industry Baxalta part of Shire
NCT02973087	3	23	2017	2020	Completed	No	Von Willebrand Disease	rVWF, Recombinant antihemophilic factor	Industry Baxalta part of Shire Baxalta Innovations GmbH, part of Shire Takeda
NCT03251872	1	6	2018	2019	Terminated	No	Pulmonary Arterial Hypertension	Olaparib	Laval University
NCT04550338	3	100	2021	2023	Not yet recruiting	No	COVID-19	Tranexamic acid	University of Alabama at Birmingham

Data retrieved from <https://clinicaltrials.gov>

RMSD = 0.294 Å

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	
1: 6YD7	0.00	0.09	0.04	0.09	0.49	0.08	0.10	0.07	0.12	0.35	0.34	0.33	0.11	0.10	0.12	0.18	0.40	0.25	0.10	0.28	0.20	0.25	0.28	0.26	4.0
2: 6YD3	0.09	0.00	0.09	0.04	0.50	0.09	0.07	0.07	0.08	0.34	0.33	0.31	0.12	0.13	0.13	0.20	0.43	0.26	0.11	0.28	0.17	0.25	0.27	0.26	3.5
3: 6YD4	0.04	0.09	0.00	0.09	0.49	0.09	0.10	0.08	0.12	0.33	0.33	0.31	0.11	0.10	0.12	0.18	0.40	0.25	0.10	0.28	0.19	0.25	0.28	0.26	3.0
4: 6YD2	0.09	0.04	0.09	0.00	0.50	0.09	0.07	0.07	0.07	0.35	0.34	0.32	0.11	0.12	0.13	0.19	0.42	0.26	0.11	0.27	0.17	0.25	0.27	0.26	2.5
5: 4Z2A	0.49	0.50	0.49	0.50	0.00	0.50	0.50	0.50	0.51	0.61	0.60	0.60	0.49	0.49	0.49	0.41	0.36	0.40	0.50	0.41	0.52	0.43	0.45	0.44	2.0
6: 6HZA	0.08	0.09	0.09	0.09	0.50	0.00	0.07	0.05	0.10	0.36	0.36	0.34	0.11	0.10	0.10	0.19	0.41	0.25	0.10	0.28	0.20	0.27	0.29	0.27	1.5
7: 6HZB	0.10	0.07	0.10	0.07	0.50	0.07	0.00	0.06	0.07	0.34	0.33	0.32	0.11	0.12	0.11	0.19	0.43	0.25	0.10	0.26	0.17	0.25	0.27	0.26	1.0
8: 6HZD	0.07	0.07	0.08	0.07	0.50	0.05	0.06	0.00	0.08	0.35	0.35	0.33	0.10	0.10	0.11	0.18	0.42	0.25	0.09	0.27	0.18	0.25	0.28	0.26	0.5
9: 6HZC	0.12	0.08	0.12	0.07	0.51	0.10	0.07	0.08	0.00	0.34	0.32	0.31	0.12	0.14	0.13	0.20	0.44	0.26	0.11	0.27	0.16	0.25	0.26	0.26	0.0
10: 6HLB	0.35	0.34	0.33	0.35	0.61	0.36	0.34	0.35	0.34	0.00	0.09	0.07	0.37	0.38	0.38	0.37	0.52	0.40	0.34	0.42	0.34	0.40	0.40	0.40	
11: 6HLD	0.34	0.33	0.33	0.34	0.60	0.36	0.33	0.35	0.32	0.09	0.00	0.07	0.36	0.38	0.37	0.36	0.52	0.40	0.34	0.40	0.32	0.38	0.38	0.38	
12: 6HLE	0.33	0.31	0.31	0.32	0.60	0.34	0.32	0.33	0.31	0.07	0.07	0.00	0.35	0.36	0.36	0.35	0.52	0.39	0.32	0.40	0.31	0.38	0.38	0.38	
13: 6EQV	0.11	0.12	0.11	0.11	0.49	0.11	0.11	0.10	0.12	0.37	0.36	0.35	0.00	0.06	0.07	0.17	0.42	0.24	0.09	0.27	0.18	0.24	0.27	0.25	
14: 6EQW	0.10	0.13	0.10	0.12	0.49	0.10	0.12	0.10	0.14	0.38	0.38	0.36	0.06	0.00	0.06	0.17	0.41	0.24	0.10	0.27	0.20	0.25	0.27	0.26	
15: 6EQX	0.12	0.13	0.12	0.13	0.49	0.10	0.11	0.11	0.13	0.38	0.37	0.36	0.07	0.06	0.00	0.17	0.42	0.24	0.10	0.27	0.19	0.24	0.27	0.25	
16: 5MIM	0.18	0.20	0.18	0.19	0.41	0.19	0.19	0.18	0.20	0.37	0.36	0.35	0.17	0.17	0.17	0.00	0.38	0.14	0.18	0.17	0.23	0.25	0.27	0.27	
17: 5JMO	0.40	0.43	0.40	0.42	0.36	0.41	0.43	0.42	0.44	0.52	0.52	0.52	0.42	0.41	0.42	0.38	0.00	0.41	0.43	0.44	0.48	0.41	0.43	0.41	
18: 5JXG	0.25	0.26	0.25	0.26	0.40	0.25	0.25	0.25	0.26	0.40	0.40	0.39	0.24	0.24	0.24	0.14	0.41	0.00	0.25	0.12	0.30	0.31	0.33	0.32	
19: 5JXH	0.10	0.11	0.10	0.11	0.50	0.10	0.10	0.09	0.11	0.34	0.34	0.32	0.09	0.10	0.10	0.18	0.43	0.25	0.00	0.26	0.17	0.25	0.27	0.26	
20: 5JXI	0.28	0.28	0.28	0.27	0.41	0.28	0.26	0.27	0.27	0.42	0.40	0.40	0.27	0.27	0.27	0.17	0.44	0.12	0.26	0.00	0.27	0.32	0.33	0.33	
21: 5JXJ	0.20	0.17	0.19	0.17	0.52	0.20	0.17	0.18	0.16	0.34	0.32	0.31	0.18	0.20	0.19	0.23	0.48	0.30	0.17	0.27	0.00	0.24	0.24	0.25	
22: 4RYD	0.25	0.25	0.25	0.25	0.43	0.27	0.25	0.25	0.25	0.40	0.38	0.38	0.24	0.25	0.24	0.25	0.41	0.31	0.25	0.32	0.24	0.00	0.09	0.08	
23: 40MC	0.28	0.27	0.28	0.27	0.45	0.29	0.27	0.28	0.26	0.40	0.38	0.38	0.27	0.27	0.27	0.27	0.43	0.33	0.27	0.33	0.24	0.09	0.00	0.09	
24: 40MD	0.26	0.26	0.26	0.26	0.44	0.27	0.26	0.26	0.26	0.40	0.38	0.38	0.25	0.26	0.25	0.27	0.41	0.32	0.26	0.33	0.25	0.08	0.09	0.00	

Supplemental Figure 3. Pairwise alignment matrix for the backbone alpha carbon atoms of the 465 common residues of 24 crystal structures of furin.

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